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Our efforts in the past year were devoted to improving our electrostatics methodology and to applying our program, DelPhi, to a new set of problems. The program has been extended so that it can now treat the non-linear Poisson-Boltzmann equation and, in addition, we have found a way to extract electrostatic contributions to solvation energies from the potentials that are calculated. We have used these two developments in the calculation of the solvation energies of small charged molecules and in the numerical description of the ion atmosphere around DNA. In another application we have calculated the ionic strength dependence of pK changes induced in the active site of the protein subtilisin from point mutations in distal charged residues.

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ANNUAL REPORT (9/1/87 - 8/31/88)

THE ELECTRICAL POTENTIAL OF PROTEINS
Contract # N00014-86-K-0483

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RESEARCH SUMMARY

The DelPhi program - We have developed our package of programs, known as DelPhi, to the point where it can be distributed to other researchers. It will be marketed commercially by BIOSYM and we will be giving it out ourselves to non-profit institutions. DelPhi calculates the electrical potential of molecules through a numerical solution to the Poisson-Boltzmann equation. A description of its capabilities was published in Protein Structure, Folding and Design 2, (the second UCLA symposium volume edited by Dale Oxender). Its first application was to superoxide dismutase as described in last year's annual report.

pK changes in subtilisin - We published in NATURE that we had succeeded in reproducing the pK changes (including their ionic strength dependence) induced in the active site of subtilisin resulting from site-directed-mutagenesis of residues about 15 Å away. The close agreement between theory and experiment at a range of ionic strengths lends confidence both to our theoretical model and to the precision of the numerical solution to the Poisson-Bolztmann equation. It should be pointed out that in applying the DelPhi program to problems of this type one need not consider the electrical potential of the entire protein but rather the effect of only a single source charge. The protein is treated as a low dielectric region and as such influences the electrical potential of the isolated charge. One of the general conclusions from this study is that electrical interactions tend to proceed though the high dielectric solvent rather than through the low dielectric protein. A useful analogy which makes this behavior understandable is that the protein acts as an insulator while the solvent acts as a conductor.

Charge-solvent interactions with continuum methods - In our previous work we had considered only the electrostatic interactions between pairs of charges. However, in order to calculate the binding energies of charged species or the total conformational energy of a molecule it is necessary to account for the interactions of individual charges with the solvent. For example the loss of solvation energy of charged

substrates upon binding to a macromolecule is approximately energetically equivalent to the gain in Coulombic energy that may drive the association. In a recent paper we showed how it is possible to use the DelPhi program to calculate electrostatic contributions to solvation and binding energies with at least comparable accuracy and orders of magnitude greater computational efficiency than free energy simulations. The work is in press in PROTEINS. It was found that charge-solvent interactions, which are frequently neglected in conformational analysis or in calculating binding energies can make extremely large contributions to the total energy of a macromolecular system.

The electrostatic potential of B-DNA - In order to treat nucleic acids as well as proteins, we extended our numerical method so that it could solve the non-lnear Poisson-Boltzmann equation. The high charge density of nucleic acids renders invalid the standard assumption that electrical potentials are much less than kT. Electrical potentials around DNA were obtained by solving the non-linear Poisson-Boltzmann equation. The detailed charge distribution and the shape of the dielectric boundary between macromolecule and solvent were explicitly taken into account. Electrical potentials and ion concentrations were compared to those obtained with simpler models. It was found that the shape of the dielectric boundary between the macromolecule and the solvent has significant effects on the calculated potentials, particularly in the grooves. Sequence specific patterns are found, the the most surprising result being the existence of positive regions of potential near the bases in both the major and minor grooves. The effect of solvent and ionic atmosphere screening of phosphate-phosphate repulsions was studied and an effective dielectric constant appropriate for molecular mechanics simulations was derived.

PUBLICATIONS (supported by ONR)

M. Gilson and B. Honig "Calculation of the Electrostatic Potential in an Enzyme Active Site". NATURE 330:84-86 (1987).

K. Sharp, M. Gilson, R. Fine and B.Honig "Electrostatic Interactions in Proteins" in Protein Structure, Folding and Design, 2:235-244 (1987).

M. Gilson and B.Honig "Calculation of the Total Electrostatic Energy of a Macromolecular System: Solvation Energies, Binding Energies and Conformational Analysis". PROTEINS (in press).

B. Jayaram, K. Sharp and B. Honig "The Electrostatic Potential of B-DNA" BIOPOLYMERS (in press).